**Remarks/Arguments:**

1. Remarks:

a. Response is timely.

A response to the Office Action was due on May 16, 2005. The applicants attach hereto a Petition For Extension Of Time Under 37 CFR 1.136(a) along with payment of the associated fee. With the three-month extension of time to respond to the Office Action, a response to it becomes due on August 16, 2005. This response was filed on this date and is therefore timely.

b. Fees.

The applicants attach hereto a completed Credit Card Payment Form for the:

(1) $1,020.00 fee associated with the filing of a Petition For Extension Of Time Under 37 CFR 1.136(a) for 3 additonal months to respond to the Office Action,

(2) $260.00 fee associated with the filing of 2 terminal disclaimers,

(3) $180.00 fee associated with the filing of a supplemental Information Disclosure Statement, and

(4) $50.00 fee for 1 claim added by amendment.

The total of the above fees is $1,510.00.

The applicants do not believe that any additional fees are due. However, please charge any additional fees required or credit any fees overpaid to Deposit Account No. 50-0244.

c. Amendments.

Claims 9 and 10 were canceled without prejudice or disclaimer.

Claims 5 and 11 were amended without prejudice or disclaimer and to further Applicants' business interests and the prosecution of the present application. The amendment to claim 5 incorporates the limitations of canceled claims 9 and 10, and, therefore is supported by the specification. The amendment to claim 11 changes its dependency to pending claim 8 from canceled claim 10.

Claim 44 was added as new claim. The addition of new claim 44 is supported in the specification at page 17, line 25 to page 18, line 23.

The amendments to the claims 5 and 11 and addition of new claim 44 as discussed above do not add any new matter. Applicant reserves the right to prosecute any canceled or amended subject matter in a later application.

2. Arguments.

According to the Office Action, mailed February16, 2005 (hereinafter, "Office Action"), claims 5, and 8 to 11 are currently pending and under examination. In the Office Action, the Examiner made the following new arguments, objections and rejections:

a. Rejection of claims - 35 USC § 103(a).

In the Office Action, three separate rejections under 35 USC § 103(a) were maintained. Claims 5 and 8 were rejected under 35 USC § 103(a) as being unpatentable over Bass (Bass et al., *J. Bacteriology*, 178:1154-1161, in view of the 1998 Article (Loosmore et al., *Infection and Immunity*, 66(3): 899-906), and Spaete (U.S. Patent No. 5,474,914 issued to Richard Spaete). According to the Examiner, Claims 5 and 8 to which this rejection is directed claims expression vectors for expression of a recombinant protein, with the expression vector comprising nucleic acids encoding a non-proteolytic mutant of the Hin47 protein (with substitutions at one of the positions, 91, 121 or 197), an additional recombinant protein, and comprising a regulatory element operatively connected to each of the nucleic acids. Claim 9 was rejected under 35 USC § 103(a) as being unpatentable over Bass, in view of the 1998 Article and Spaete, and further in view of Barenkamp (Barenkamp and St. Geme III, Molecular Microbiology, 19: 1215-1223) and the 182 Patent (U.S. Patent No. 6,335,182). According to the Examiner, claim 9 is directed to an expression vector encoding a non-proteolytic Hin47 analog, a regulatory element, and an additional nucleic acid molecule coding for another recombinant protein, wherein that recombinant protein is the *Haemophilus influenzae* Hia protein. Claim 10 was rejected under 35 USC § 103(a) as being unpatentable over Bass, in view of the 1998 Article, Spaete, Barenkamp, and in further view of St. Geme (WO 96/30519). According to the Examiner, claim 10 is directed to the claimed expression vectors wherein the recombinant polypeptide is an N-terminally truncated Hia protein. The Applicants have canceled claims 9 and 10. As such, the 35 USC § 103(a) rejections noted above are moot. This leaves the 35 USC § 103(a) of claim 5.

The Applicants have amended claim 5 to incorporate the limitations of claims 9 and 10. With this amendment, claim 5 is now directed to:

An expression vector for expression of a recombinant protein in a host cell, comprising:

a nucleic acid molecule encoding a non-proteolytic mutant of a *Haemophilus* Hin47 protein wherein said Hin47 protein is mutated at amino acid 91, 121 or 197 and said nucleic acid molecule includes a portion encoding the leader sequence for said non-proteolytic mutant,

at least one additional nucleic acid molecule encoding the recombinant protein, wherein the recombinant protein is a Hia protein of a strain of *Haemophilus influenzae* which is N-terminally truncated, and

at least one regulatory element operatively connected to said first nucleic acid molecule and at least one regulatory element operatively connected to said at least one additional nucleic acid molecule to effect expression of at least said recombinant protein in the host cell.

Because of the amendment made which incorporates the limitations of claim 9 and 10 into claim 5, the Applicants will address below the 35 USC § 103(a) rejections discussed above as if they applied to amended claim 5 and its dependent claim 8.

I

Section 2142 of the MPEP states: "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

The Applicants, in response to the 35 USC § 103(a) rejections of claims 5, 8, 9 and 10 made in the office action, dated July 13, 2005, have argued in the main that these claims would not be obvious to one of ordinary skill in the art because the combination of references (Bass, the 1998 Article and Spaete) cited by the Examiner in the rejections when combined do not teach all of the limitations of the claims and because they do not provide a reasonable expectation of success in using the non-proteolytic mutant Hin47 protein (disclosed in the Instant Application) as a chaperone protein. These rejections have been maintained in the instant Office Action.

II

In the instant Office Action, the Examiner responded to the Applicants' arguments made in response to the the instant rejection in the office action, dated July 13, 2004. The Applicants' two arguments according to the Examiner are: (1) the prior art does not teach the inclusion of the leader sequence as required by the amended claims and (2) the prior art does not provide adequate teachings so that there is a reasonable expection of success in the use of a recombinant non-proteolytic mutant Hin47 protein as a chaperone protein. In response to the Applicant's first argument, the Examiner alleges it would be recognized by those in the art that the naturally occurring leader sequence of Hin47 would be effective as a functional equivalent of the leader sequences of Spaete if the vector was to be expressed in a bacterium; and, in such a system, the bacterial cell would be able to naturally process the leader sequence of Hin47, and would not require the artificial processing site suggested for use in the yeast expression system of Spaete. In response to the Applicants' second argument, the Examiner alleges specific teachings in the art indicate that the non-proteolytic Hin47 mutants may be used as carriers for recombinantly expressed proteins citing U.S. Patent No. 5,656,436 (column 7, lines 35-53) and WO 96/03506 (pages 3, 6, and 14-15, and claim 52). The Applicants respectfully traverse this rejection of claims 5 and 8.

First, as noted above, the Examiner alleges it would be recognized by those in the art that the naturally occurring leader sequence of Hin47 would be effective as functional equivalent of the leader sequences of Spaete if the vector was to be expressed in a bacterium; and, in such a system, the bacterial cell would be able to naturally process the leader sequence of Hin47, and would not require the artificial processing site suggested for use in the yeast expression system of Spaete. The Applicants respectfully request that the Examiner provide the citations in the prior art supporting the allegation.

Second, as noted above, the Examiner alleges the Applicants' argument that the art does not provide adequate teachings so that there is a reasonable expectation of success in the use of a non-proteolytic mutant Hin47 protein as a chaperone is not persuasive. This is because there are specific teachings in the art which indicate that the non-proteolytic mutant Hin47 protein may be used as carriers for recombinantly expressed proteins. The Examiner cited as support U.S. Patent No. 5,656,436 (column 7, lines 35-53) and WO 96/03506 (pages 3, 6, and 14-15, and claim 52). U.S. Patent No. 5,656,436, at column 7, lines 35-53, states:

> In additional embodiments of the present invention, the Hin47 analogs having reduced protease activity as provided herein may be used as carrier molecules to prepare chimetic

> molecules and conjugate vaccines (including glycoconjugates) against pathogenic bacteria, including encapsulated bacteria. Thus, for example, glycoconjugates of the present inventions may be applied to vaccinations to confer protection against disease and infection caused by any bacteria having polysaccharide antigens including lipooligosaccharides (LOS) and PRP. Bacterial pathogens may include; for example, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Escherichia coli*, *Neisseria meningitidis*, *Salmonella typhi*, *Streptococcus mutans*, *Cryptococcus neoformans*, *Klebsiella*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Particular antigens which can be conjugated to analogs of Hin47 and methods to achieve such conjugations are described in applicants published PCT application WO 94/12641 which is hereby incorporated by reference thereto. [underline added for emphasis]

and WO 96/03506, page 14-15, states, in pertinent part, that:

> ...The provided analogs also may be used as a carrier protein for hapten, polysaccharides or peptides to make a conjugate vaccine against antigenic determinants unrelated to Hin47. [underline added for emphasis]

With respect to the above, the Applicants respectfully submit that a protein (such as the non-proteolytic Hin47 of the Instant Application) acting as carrier would be different than the same acting as a chaperone because the former requires a covalent linkage joining a hapten, polysaccharide, peptide or protein to the carrier protein, while the latter requires a non-covalent binding interaction between the chaperone protein and another protein that it is thought to bind to. As a carrier protein, a non-proteolytic mutant Hin47 protein would either be chemically coupled through a covalent bond or fused by genetic engineering methods again through a covalent bond to another protein or peptide. For example, WO 94/12641 (cited in the above quotation), at page 25, line 9 through line 30, states:

> In another embodiment, the present invention provides a gene coding for the outer membrane protein D15 from *H. influenzae* having the specific nucleotide sequences described herein or ones substantially homologous thereto (i.e. those which hybridize under stringent conditions to such sequences), for genetically engineering hybrids or chimeric proteins containing a D15 fragment fused to another polypeptide or protein or a polysaccharide, such as *H. influenzae* outer membrane proteins, for example, P1, P2, or P6 or PRP. As a result, the hybrids, chimeric proteins or glycoconjugates may have higher protectivity against *H. influenzae* than D15, or P1, or P2, or P6, or PRP alone.
>
> Thus, D15 outer membrane protein can function both as a protective antigen and as a carrier in a conjugate vaccine to provide autologous T- cell priming, wherein the hapten part of the conjugate is the capsular polysaccharide moiety (PRP) of *H. influenzae*. This D15 carbohydrate conjugate can elicit antibodies against both PRP and D15, and thus should enhance the level of protection against *H. influenzae*-related diseases, especially in infants. [underline added for emphasis]

Further, at page 27, line 31, WO 94/12641 states that U.S. Patent No. 4,599,230 is incorporated by reference as an example of vaccines containing peptides. In this U.S. patent, column 23, line 7 through column 24, line 2, states:

> The synthetic polypeptides were coupled to keyhole limpet hemocyanin (KLH) or tetanus toxoid (TT) by either of the following two methods. In the first method, the carrier was activated with m-maleimidobenzoyl-N-hydroxysuccinimide ester and was subsequently coupled to the polypeptide through a cysteine residue added to the amino- or carboxy-terminus of the polypeptide, as described in Liu et al., Biochem., 80, 690 (1979). In the second method, the polypeptide was coupled to the carrier through free amino groups, using a 0.04 percent glutaraldehyde solution as is well known. See, for example, Klipstein et al., J. Inpect. Disc., 147, 318 (1983).
>
> As discussed before, cysteine residues added at the amino- and/or carboxy-termini of the synthetic polypeptide have been found to be particularly useful for forming conjugates via disulfide bonds and Michael addition reaction products, but other methods well known in the art for preparing conjugates can also be used. Exemplary additional binding procedures include the use of dialdehydes such as glutaraldehyde (discussed above) and the like, or the use of carbodiimide technology as in the use of a water-soluble carbodiimide, e.g. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, to form amide links to the carrier.
>
> Useful carriers are well known in the art and are generally proteins themselves. Exemplary of such carriers are keyhole limpet hemocyanin (KLH), edestin, thyroglobulin, albumins such as bovine serum albumin or human serum albumin (BSA or HSA, respectively), red blood cells such as sheep erythrocytes (SRBC), tetanus toxoid, cholera toxoid as well as polyamino acids such as poly(D-lysine:D-glutamic acid), and the like.
>
> As is also well known in the art, it is often beneficial to bind the synthetic polypeptide to its carrier by means of an intermediate, linking group. As noted above, glutaraldehyde is one such linking group. However, when cysteine is used, the intermediate linking group is preferably an m-maleimidobenzoyl N-hydroxysuccinimide ester (MBS). MBS is typically first added to the carrier by an ester-amide interchange reaction. Thereafter, the above Michael reaction can be followed, or the addition can be followed by addition of a blocked mercapto group such as thiolacetic acid (CH.sub.3 COSH) across the maleimido-double bond. After cleavage of the acyl blocking group, and a disulfide bond is formed between the deblocked linking group mercaptan and the mercaptan of the added cysteine residue of the synthetic polypeptide.
>
> The choice of carrier is more dependent upon the ultimate intended use of the antigen than upon the determinant portion of the antigen, and is based upon criteria not particularly involved in the present invention. For example, if a vaccine is to be used in animals, a carrier that does not generate an untoward reaction in the particular animal should be selected. If a vaccine is to be used in man, then the overriding concerns involve the lack of immunochemical or other side reaction of the carrier and/or the resulting antigen, safety and efficacy--the same considerations that apply to any vaccine intended for human use.

In view of the above, the Applicants respectfully submit that the Examiner's conclusion that there is a reasonable expection of success in the use of a recombinant non-proteolytic mutant Hin47 protein as a chaperone protein is not supported by the reasoning that there are specific teachings in the art which indicate that the non-proteolytic mutant Hin47 protein may be used as carriers for recombinantly expressed proteins, as exemplified by U.S. Patent No. 5,656,436 (column 7, lines 35-53) and WO 96/03506 (pages 3, 6, and 14-15, and claim 52). This is because the specific teaching in the art are said to be exemplified by U.S. Patent No. 5,656,436 and WO 96/03506 relate to methods of covalently linking a hapten, polysaccharide, peptide or protein to the carrier protein, instead of a non-covalent binding interaction between the chaperone protein and another protein that it is thought to bind to.

III

The Applicants note that each of the three 35 USC § 103(a) rejections made in the Office Action relies on the teachings of Bass, as supported by the teachings of Spiess et al., *Cell*, 97:337-347 (April 1999)) and Faccio et al., *J. Biol. Chem.*, 275(4): 2581-2588 (January 2000). In a prior office action, dated November 17, 2003, the Examiner alleged that Bass teaches that Hin47 is useful as a chaperone protein and when combined with the teaching of the 1998 Article, the combination teaches that a non-proteolytic form of Hin47 (as described in the Instant Application) may be used as a chaperone protein. In the subsequent office action, dated July 13, 2004, Examiner went on to allege that the Bass reference indicates that the HtrA/DepG proteins represent a family of proteins; and, as such, the teachings of this reference for one such of these proteins would be indicative of the behavior of other members of the family, and that the teachings of the 1998 Article, Spiess and Faccio support this view. Having said this, the Examiner concluded:

> Thus, the art recognizes a relationship among the HtrA/DepG proteins, and indicates that non-proteolytic HtrA proteins generally, and not those of any specific bacterium, would be effective as chaperones.

The Applicants in response to the 35 USC § 103(a) rejections made in the prior office actions respectfully traversed them. The Applicants argued in the main that the rejected claims would not be obvious to one of ordinary skill in the art because the combination of references (Bass, the 1998 Article and Spaete) cited by the Examiner in the rejections do not teach all of the limitations of the claims and because they do not provide a reasonable expectation of success in using the non-proteolytic mutant Hin47 protein (disclosed in the Instant

Application) as a chaperone protein. In response to the instant 35 USC § 103(a) rejections, the Applicants respectfully maintain the arguments previously made.

In addition, the Applicants respectfully submit the rejected claims would not be obvious to one of ordinary skill in the art because the combination of references (Bass, the 1998 Article and Spaete) cited by the Examiner do not provide a reasonable expectation of success in using the non-proteolytic mutant Hin47 protein (disclosed in the Instant Application) as a chaperone protein because of the teaching of Kim et al. (*J. Mol. Biol.*, Vol. 294, pp. 1363-1374 (Dec. 1999)) that HtrA may exert its chaperone function toward specific target proteins rather than acting as a general chaperone. This reference is provided in the attached Supplemental Information Disclosure Statement. Kim et al., at page 1371, left column, first full paragraph, in pertinent part, states:

> Recently, Spiess *et al.* (1999) has demonstrated that HtrA has a new function as a chaperone at low temperatures. They also showed that proteolytically inactive HtrA/S210A stimulates the refolding of MalS at both 37 and 42°C. In our experiments, however, HtrA/S210A failed to protect the thermal aggregation of CS or MDH at 43°C or the aggregation of insulin B-chain after reduction by DTT at 35°C (data not shown and see Figure 6). On the other hand, wild-type HtrA prevented the formation of aggregated proteins by rapid degradation of unfolded intermediates under the same experimental conditions. Thus, HtrA may exert its chaperone function toward specific target proteins rather than acting as a general chaperone.

Thus, it can be seen that the teaching of Kim et al. would raise doubt in the mind of one with ordinary skill in the art whether the N-terminally truncated Hia proteins (as disclosed in the Instant Application) would be bound at all in a chaperone-like manner by the non-proteolytic mutant Hin47 proteins (also disclosed in the Instant Application) because the latter may lack specificity for the former as a binding partner. Put differently, in view of the teaching of Kim et al. as it relates to Spiess, it would not be clear to one with ordinary skill in the art that the non-proteolytic mutant Hin47 proteins would be chaperones of the N-terminally truncated Hia proteins. Accordingly, it cannot be said that the teachings of Bass, as supported by the teachings of Spiess et al., *Cell*, 97:337-347 (April 1999)) and Faccio et al., *J. Biol. Chem.*, 275(4): 2581-2588 (January 2000), in combination with the 1998 Article, would lead to the conclusion (as it applies to amended claims 5 and 8) made by the Examiner that:

> Thus, the art recognizes a relationship among the HtrA/DepG proteins, and indicates that non-proteolytic HtrA proteins generally, and not those of any specific bacterium, would be effective as chaperones.

For this reason, and the reasons provided in responses to the previous office actions relating to the 35 USC § 103(a) rejections based on the combination of the cited references (Bass, the 1998 Article and Spaete), the Applicants respectfully submit that this combination of references does not provide a reasonable expectation of success in using the non-proteolytic mutant Hin47 protein (disclosed in the Instant Application) as a chaperone protein.

Furthermore, the Applicants also respectfully submit that, in view of Kim et al., any suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings (Bass, the 1998 Article and Spaete) would be undercut. This is because any such suggestion or motivation to combine the references relating to non-proteolytic mutant Hin47 proteins and relating to Hia proteins must be either dimished or abrogated, as Kim et al. teaches that HtrA may exert its chaperone function toward specific target proteins as opposed to being a general chaperone.

IV

In view of the above arguments, the Applicants respectfully request that the 35 USC § 103(a) rejections as they apply to claim 5 and 8 be withdrawn.

d. Rejection of claims 5 and 8 – Nonstatury Double Patenting.

Claims 5 and 8 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10, 17 and 19 of U.S. Patent No. 5,939,297.

The applicants attach hereto a terminal disclaimer relating to U.S. Patent No. 5,939,297. Accordingly, the applicants respectfully request that this rejection be withdrawn.

e. Rejection of claims 5 and 8 – Nonstatury Double Patenting.

Claims 5 and 8 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5 and 6 of U.S. Patent No. 6,025,342.

The applicants attach hereto a terminal disclaimer relating to U.S. Patent No. 6,025,342. Accordingly, the applicants respectfully request that this rejection be withdrawn.

f. Rejection of claim 9 – Nonstatury Double Patenting.

Claim 9 was rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over 1, 5 and 6 of U.S. Patent No. 6,025,342 or claims 10, 17 and 19 of U.S. Patent No. 5,939,297, further in view of Barenkamp and St. Geme III, Molecular Microbiology, 19: 1215-1523.

As the applicants have attached hereto a terminal disclaimer relating to U.S. Patent No. 6,025,342 and a terminal disclaimer relating to U.S. Patent No. 5,939,297, the applicants respectfully request that this rejection be withdrawn.

3. Conclusions.

The amendments, remarks and arguments submitted herein are intended to be fully responsive to the outstanding Office Action, to advance the prosecution of the present invention, and to place the application in condition for allowance.

The applicants respectfully request consideration and entry of this paper. The applicants also respectfully request reconsideration of this application, as amended, and issuance of a timely Notice of Allowance in this case. Should the Examiner have any questions concerning this application, he/she is invited to contact the undersigned at (570) 839-5537.

Respectfully submitted,

Date: August 16, 2005

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